Translational Control Mediates Lifespan Extension Due to Dietary Restriction in *Drosophila*

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Abstract

Aging is characterized by the declining ability of an organism to maintain homeostasis, which eventually leads to death. Dietary restriction (DR), the reduction of nutrients without malnutrition, extends lifespan in various organisms, yet its molecular underpinnings are poorly understood. We show that in *Drosophila,* DR upregulates the translational repressor 4EBP, the eukaryotic translation initiation factor 4E binding protein, and that this upregulation is necessary for the full lifespan extension upon DR and sufficient to extend lifespan on a nutrient rich diet. Investigation of the genome-wide translational changes upon DR using translation state array analysis (TSAA) found that translationally downregulated genes tend to have extensive 5' untranslated regions (UTR) secondary structures, while those that are upregulated have weakly structured 5'UTRs. Among the translationally upregulated genes, mitochondrial ribosomal proteins and electron transport chain components were overrepresented. Mitochondrial genes were found to have weakly structured 5'UTRs in *Drosophila,* and this was conserved in Humans. The 5'UTRs of mitochondrial genes were found to be sufficient to confer preferential translation during times of high 4EBP activity in a cap-independent manner to reporter constructs. Upregulation of mitochondrial function was verified and found to be *d4EBP* dependent, implicating a novel mechanism for regulating mitochondrial function upon DR. These results implicate mRNA translation initiation in modulating lifespan and mitochondrial function upon DR.

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